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REVIEW

A Systematic Review of Ultrasound-Detected Lipohypertrophy in Insulin-Exposed People with Diabetes

Haya Abu Ghazaleh  · Rabab Hashem · Angus Forbes ·
Thandiwe Rebecca Dilwayo · Maria Duaso · Jackie Sturt ·
Susan Halson-Brown · Henrietta Mulnier

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ABSTRACT

Introduction: Lipohypertrophy (LH) is a common complication occurring in diabetes individuals. The most common methods used include palpation, visual examination and/or ultrasound (US). To date, there is limited information on the detection sensitivity among the different techniques used to identify LH. This systematic review aimed to identify studies that examined insulin-related LH using US detection to identify the prevalence, characteristics and morphology of LH, and to compare US and clinical palpation methods for detecting LH.

Methods: Three electronic databases were systematically searched for studies detecting LH

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H. Abu Ghazaleh (✉) · R. Hashem · A. Forbes ·
T. R. Dilwayo · M. Duaso · J. Sturt · H. Mulnier
Florence Nightingale Faculty of Nursing and
Midwifery, King's College London, London, UK
e-mail: haya.abu_ghazaleh@kcl.ac.uk

S. Halson-Brown
Department of Women and Children's Health,
School of Life Course Sciences, King's College
London, St. Thomas' Hospital, London, UK

using US in insulin users. Articles were screened for eligibility and included studies were appraised using quality assessment tools. The quality of the evidence was evaluated using Grading of Recommendations Assessment, Development and Evaluation, and the extracted data was synthesised narratively.

Results: Sixteen articles were included in the review providing data on 1722 patients. The prevalence of LH prevalence varied from 14.5% to 88% (median 56.6%). Identified risk factors for the development of included insulin injection behaviour such as a lack of injection site rotation and social factors such as low education level. Four studies compared LH detection by US to palpation, providing inconsistent results. One study showed that palpation detected 64% more LH, whilst two studies demonstrated that US identified 50% more sites and extended areas of LH (additional ~ 5 cm²). Another study provided comparable estimates between palpation and US in clinicians trained to detect LH (97%).

Conclusion: The evidence highlights a lack of congruence in results pertaining to the detection sensitivity of US and palpation for LH sites. More research with robust study design is needed to verify whether clinically palpation is sufficient to detect LH, or whether US would increase the precision of LH assessment to help address this common clinically significant problem.

Keywords: Hypertrophy; Insulin injection; Lipohypertrophy; Palpation; Ultrasound

INTRODUCTION

Lipohypertrophy (LH) occurs in subcutaneous tissue as a result of the lipogenic effect of repeated insulin exposure [1, 2]. The fat cells enlarge and proliferate resulting in thickened tissue, sometimes forming lumps under the skin. LH is associated with suboptimal glycaemic control, with one recent study reporting a threefold higher incidence of LH in patients whose control was above the current national target ($\text{HbA1c} \geq 7\%$, 86 mmol/L), compared to those within the target range [3]. Injecting insulin into an LH lesion has been shown to attenuate insulin action with consequent excess glucose exposure, glycaemic variability and increased risk of severe hypoglycaemia [4–6]. Known risk factors for the development of LH include high BMI (≥ 25), frequent needle reuse, failure to rotate insulin injection sites effectively, size of rotation area, level of education, and duration of insulin exposure [3, 7, 8]. It is also likely that patient behaviours are significant mediators in the level of LH observed, with patients reusing sites that are less painful or because a site is more convenient to access [9, 10].

Increasing awareness of the importance of LH in diabetes care has led to the development of international guidelines for managing injection areas and for detecting LH [11, 12]. One recent multicentred UK study demonstrated improved injecting behaviours and metabolic outcomes following implementation of one of these guidelines in about two thirds of those exposed to the guideline [13]. However, the extent to which these guidelines are observed in routine clinical care is unknown, nor is it known how frequently or rigorously LH is assessed. It may be that there is a lack of awareness within the community of diabetes professionals and patients on the prevalence and significance of LH.

In clinical practice, LH is most commonly assessed by palpation. However, the reliability of this method is potentially low, with high levels of inter-clinician variation. This was

recently demonstrated by Gentile et al. [14], whereby nurses trained to use a more stringent palpation technique were able to show 97% detection of cases; while the comparator missed 34% of cases. As a consequence, ultrasound (US) has been proposed as a potentially more objective method for detecting LH. US may provide more precise estimates of the true prevalence of LH, as current estimates based on mainly observation or palpation are divergent with estimates ranging from 3.6% to 64%, with a median of 32.8% [14].

The aim of this systematic review was to present a summary of the additional insights into LH contributed by US detection studies by assessing the prevalence of LH, identifying factors associated with the development of LH, and providing some estimation on the sensitivity of palpation versus US in detecting LH.

METHODS

A protocol-based systematic review was used to identify studies using US to detect LH, addressing the following objectives:

- To identify the estimated prevalence, anatomical distribution and the tissue morphology of LH with US and/or palpation assessment
- To identify factors associated with LH in US assessed cases
- To estimate the sensitivity of palpation in LH detection, with US as the reference

Search Strategy

A comprehensive literature search was conducted using three electronic databases (Medline, Embase and Cinahl) to identify articles pertaining to the detection of LH using US in insulin-treated patients with diabetes mellitus. The search used both Medical Subject Headings (MeSH) and free-text synonyms for the following terms: palpation, ultrasonography, lipodystrophy, diabetes mellitus and insulin. An example search protocol is presented in Appendix 1. Additional papers were identified through free-text searches, citation searching and by reviewing secondary references.

Retrieved articles were screened by three independent researchers for their relevance (HA, RH and RD).

Selection Criteria

Studies examining the detection of LH using US with or without palpation techniques in type 1 and type 2 insulin-treated patients with diabetes were included in the literature synthesis. Publications were excluded if they discussed LH in the context of gestational diabetes, were based on visual examination only without palpation, or addressed other causes of lipodystrophy. Only data from primary studies were considered and review articles were excluded.

Data Extraction

Two review authors (HA, RD) independently extracted the data from the included studies. The main outcomes reviewed were the different forms of insulin administration resulting in LH occurrence, risk factors of LH and the detection sensitivity of LH using US and/or palpation. Additional data extracted included study design, study location and year, population, sample size, insulin exposures, patient characteristics and metabolic factors.

Data Synthesis

The data were synthesised using a narrative approach addressing the outlined review objectives. Studies were too heterogeneous to provide a meta-analysis, but study results were tabulated to provide a collective assessment of their findings.

Quality Assessment

The relevant studies identified for inclusion in the review used different methods and designs; hence, multiple appraisal tools were used to assess the scientific rigour and quality of the studies, including the Cochrane Collaboration tool for randomised controlled trials (RCTs) [15], the Quality Assessment Tool for

Observational Cohort and Cross-Sectional Studies devised by the National Institutes of Health [16], and the Joanna Briggs Institute critical appraisal checklist for case reports [17]. Two authors assessed the overall quality of the included studies (HA, RD). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was also employed to assess the quality of the estimations provided by the included studies, considering the following criteria: risk of bias; inconsistency, indirectness and imprecision; effect magnitude; dose–response effect; and other sources of potential confounders. The quality assessments were used to rate the quality of the evidence from high to very low [18].

Ethical Considerations

This article does not contain any new studies with human or animal subjects performed by any of the authors and as such no ethical approval was required.

RESULTS

The search strategy yielded 317 citations, duplicates were removed and the remaining articles were subsequently screened for their relevance based on the review inclusion criteria ($n = 284$). Reasons for exclusion included detection method not identified ($n = 5$), study did not address the review objectives ($n = 4$), or repetition of findings in multiple papers ($n = 4$). A total of 17 unique studies reported in 16 papers were selected for inclusion (Fig. 1).

The characteristics of the studies included in the literature synthesis are presented in Table 1. Most studies utilised observational designs to consider the frequency of LH in cohorts of insulin-treated patients [14, 19–30]. Four studies compared the detection sensitivities of palpation and using US as a reference standard [14, 19, 23, 29, 31]. Three individual cases of LH in patients with diabetes were presented [20, 32] and one considered the effectiveness of LH detection using three different methods using a cross-over RCT design [4]. A few studies presented data on glycaemic control and insulin

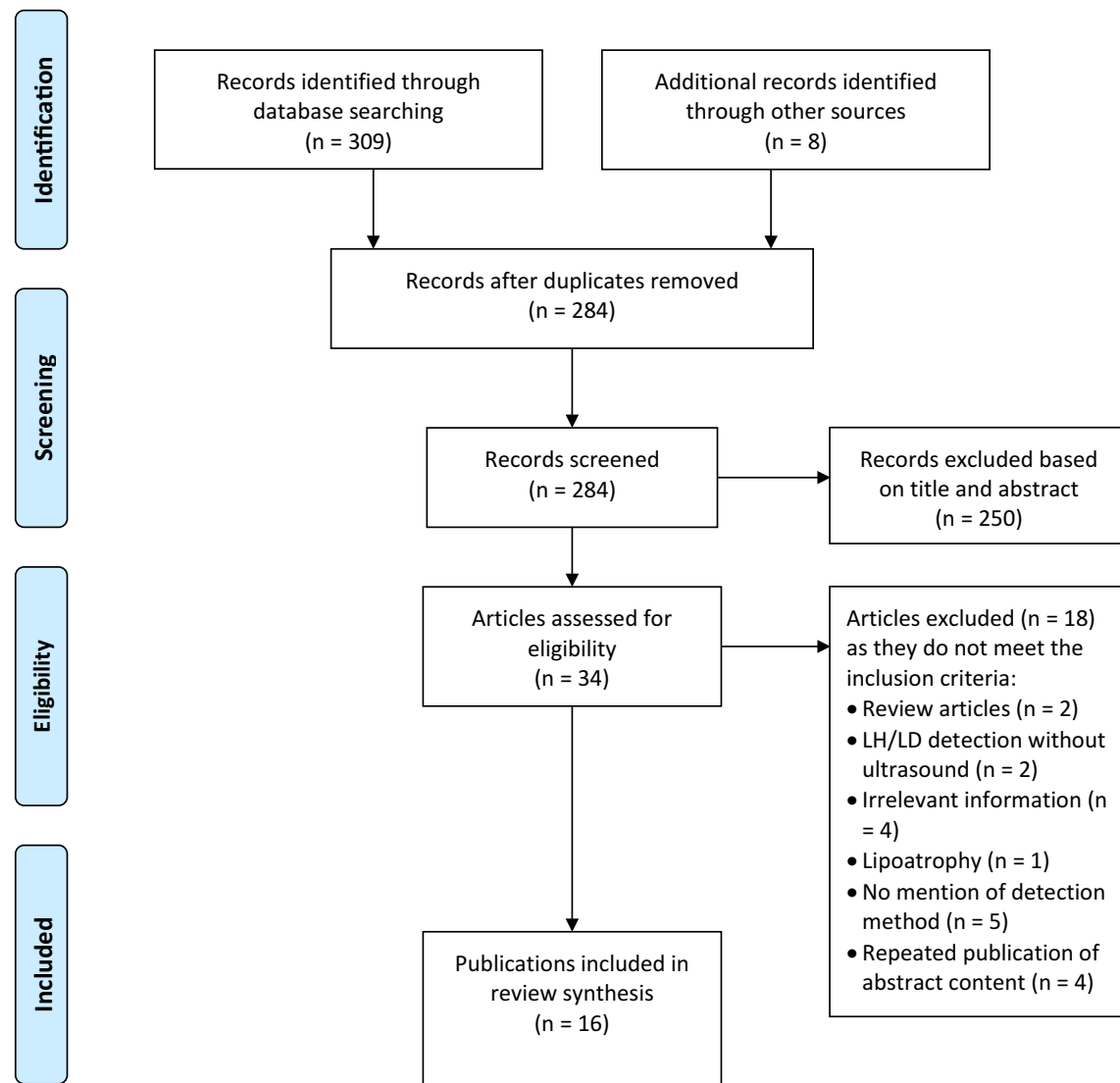


Fig. 1 PRISMA flowchart for inclusion of selected articles in this systematic review

activity following insulin administration in LH regions [4, 19, 20, 32] and risk factors in promoting LH lesions [20–22, 25, 26]. Three studies aimed to define and grade LH using US scanning [19, 24, 33]. Across the studies, insulin exposure was almost exclusively via needle injection. Thirteen studies were carried out in Europe, and two each in North America and Asia.

Quality Appraisal

The overall quality of the observational studies was poor, with information deficits in relation

to the power of the analyses undertaken and level of follow-up. Of the studies comparing palpation and US, only two mentioned blinding and only three out of the 12 observational studies were adjusted for confounders. Despite the overall poor quality of the studies, they all yielded data of relevance to the review objectives. The RCT study was identified as having a moderate rating for risk of bias, as there was a lack of information on allocation concealment and participant blinding which may have led to assessor contamination [4]. The findings of the review are presented thematically below, with tables summarising the study findings.

Table 1 Summary of included studies

Author (year), country	Study aim(s)	Sample population	Insulin therapy*	Detection method(s), assessor(s), region(s)	Outcome measure(s)
RCT					
Famulla et al. (2016) [4] Germany	Determine the impact of LH on insulin activity	Sample size: 13 Population: T1DM Mean age (years, SD): 50.1 ± 10.5 Gender (M/F): ND Mean diabetes duration (years, SD): 26.8 ± 6.9	Insulin needle injection	<i>Detection</i> Observation, palpation (pre- defined examination procedure) and US <i>Assessors</i> 2 independent investigators <i>Region</i> Abdomen	LH detection, insulin absorption in LH regions, diabetes outcomes: insulin and glucose levels
Observational studies					
Bertuzzi et al. (2017) [19] Italy	Characterisation of LH using US	Sample size: 20 Population: T1DM Mean age (years, SD): 37 ± 12 Gender (M/F): 8/12 Mean diabetes duration (years, SD): 22 ± 12	CSII, MDI	<i>Detection</i> Palpation (pre-defined criteria), US (pre-defined criteria) <i>Assessors</i> Investigators <i>Region</i> Abdomen, arm, gluteus	LH detection, metabolic parameters: HbA1c
Blanco et al. (2013) [20] Spain	Assess LH prevalence and determine its correlation with clinical and public- health factors	Sample size: 430 Population: T1DM (41%) + T2DM (59%) Mean age (years, SD): 49 ± 22.8 Gender (M/F): 221/202 Diabetes duration (years, range) 6–15	Insulin pen	<i>Detection</i> US (pre-defined characteristics) <i>Assessors</i> CD <i>Region</i> Abdomen	Prevalence of LH, risk factors of LH, diabetes outcomes: hypoglycaemia, glucose variability

Table 1 continued

Author (year), country	Study aim(s)	Sample population	Insulin therapy*	Detection method(s), assessor(s), region(s)	Outcome measure(s)
Conwell et al. (2008) [21] Canada	Describe dermatological changes with CSII therapy	Sample size: 50 Population: T1DM Mean age (years, SD): 13.3 ± 3.5 Gender (M/F): 24/26 Mean diabetes duration (years, SD): 6.5 ± 3.7	CSII	<i>Detection</i> Palpation (pre-defined criteria) in all 50 patients, US (pre-defined criteria) in 8 out of 50 patients <i>Assessors</i> 1 trained investigator <i>Region</i> Abdomen, back/buttock, legs	Frequency of LH, dermatological changes including LH
Davidenko et al. (2014) [22]—abstract, Russia	Develop estimation risk model of insulin induced LH	Sample size: 140 Population: Diabetes (NS) Mean age (years, SD): ND Gender (M/F): 51/89 Mean diabetes duration (years, SD): ND	NS	<i>Detection</i> Observation, palpation, US <i>Assessors</i> CD <i>Region</i> ND	Frequency of LH, estimation of insulin as a risk factor of LH
Gentile et al. (2016) [14] Italy	Identify inexpensive and accurate LH detection method	Sample size: 40 Population: Diabetes (NS) Mean age (years, SD): 54 ± 15 Gender (M/F): 16/24 Mean diabetes duration (years, SD): ND	Insulin needle injection	<i>Detection</i> Palpation (pre-defined criteria), US (pre-defined criteria) <i>Assessors</i> Trained vs non-trained nurses <i>Region</i> Abdomen, arm, thigh	Prevalence of LH, detection accuracy of LH between trained and non-trained HPs

Table 1 continued

Author (year), country	Study aim(s)	Sample population	Insulin therapy*	Detection method(s), assessor(s), region(s)	Outcome measure(s)
Kapeluto et al. (2015) [33]—abstract, Canada	Establish a criteria for LH detection using US	Sample size: 7 Population: Insulin-users Mean age (years, SD): ND Gender (M/F): 6/1 Mean diabetes duration (years, SD): ND	NS	Detection Palpation, US Assessors: Single team + radiologist Region: Abdomen	LH diagnostic criteria using US
Kasperska-Czyzyk et al. (2000) [23]—abstract, Poland	Determine the robustness of US in the diagnosis and characterisation of LH	Sample size: 30 Population: T1DM (33%) + T2DM (60%) + secondary diabetes (7%) Mean age (years, SEM): 60 ± 2 Gender (M/F): 16/14 Mean diabetes duration (years, SD): ND	Insulin needle injection	Detection Palpation, US Assessors: CD Region: Abdomen, arms, thighs	Detection accuracy of LH between US and palpation
Mulnier et al. (2017) [24]—abstract, UK	Evaluate the feasibility of US to detect and characterise LH	Sample size: 26 Population: T1DM Mean age (years): 41 Gender (M/F): ND Mean diabetes duration (years): 22.7	Insulin needle injection	Detection: US Assessors: CD Region: CD	LH detection, changes in subcutaneous tissue with insulin use

Table 1 continued

Author (year), country	Study aim(s)	Sample population	Insulin therapy*	Detection method(s), assessor(s), region(s)	Outcome measure(s)
Nasser et al. (2017) [25] Bahrain	Determine LH prevalence and risk factors of LH	Sample size: 95 Population: T1DM (3%) + T2DM (97%) Age (years, range): 40 to ≥ 70 Gender (M/F): 23/72 Diabetes duration (years, range): 5 to ≥ 20	Insulin needle injection	Detection: US Assessors: Clinical nurse Region: Abdomen, arm, thigh	Prevalence of LH, risk factors of LH
Patrakeeva et al. (2014) [26]— Abstract, Russia	Evaluate LH frequency using different insulin regimens and risk factors of LH	Sample size: 29 Population: T1DM Mean age (years, SD): 27 ± 4 Gender (M/F): ND Mean diabetes duration n (years, SD): 13.7 ± 2.1	CSII, MDI	Detection: US Assessors: ND Region: ND	Prevalence of LH, risk factors of LH
Percium (2010) [27] Romania	Characterise LH sites using US	Sample size: 40 Population: Diabetes (NS) Age (years, range): 15 – 65 Gender (M/F): 14/26 Mean diabetes duration (years, SD): ND	Insulin needle injection	Detection palpation (pre-specified criteria), US (pre-specified criteria) Assessors ND Region Abdomen, arm, thigh, buttocks	Diagnosis and evaluation of LH sites

Table 1 continued

Author (year), country	Study aim(s)	Sample population	Insulin therapy*	Detection method(s), assessor(s), region(s)	Outcome measure(s)
Perciu et al. (2014) [28] Romania	Compare the diagnosis of dystrophies between US and palpation	Sample size: 53 Population: T1DM Age (years, range): 2–15 Gender (M/F): 33/20 Diabetes duration (years, range): 1–13	Insulin needle injection	<i>Detection</i> Palpation (pre-specified criteria), US (pre-specified criteria) <i>Assessors</i> CD <i>Region</i> Abdomen, arm, thigh, buttocks	Frequency of hypertrophic sites
Volkova et al. (2013) [29]—abstract, Russia	Compare the frequency of LH between US and palpation	Sample size: 215 Population: Diabetes (NS) Mean age (years): 46 Gender (M/F): 142/73 Mean diabetes duration (years, SD): ND	Insulin needle injection	<i>Detection</i> : Observation, palpation, US <i>Assessors</i> : ND <i>Region</i> : Paraumbilical/buttocks, hips, shoulders	Detection accuracy of LH between US and palpation
Wang et al. (2014) [30]—abstract, China	Estimation of skin and subcutaneous layer thickness and prevalence of LH	Sample size: 509 Population: T1DM + T2DM (% NS) Age (years, range): 18–85 Gender (M/F): ND Diabetes duration (years, SD): ≥ 1	Insulin needle injection	<i>Detection</i> US <i>Assessors</i> ND <i>Region</i> Abdomen, arm, thigh, buttocks	Prevalence of LH, estimation risk of subcutaneous and intramuscular injection

Table 1 continued

Author (year), country	Study aim(s)	Sample population	Insulin therapy*	Detection method(s), assessor(s), region(s)	Outcome measure(s)
Case reports					
Blanco et al. (2013) [20] Spain	Assess diabetes history of LH patient	Sample size: 1 Population: T1DM Age (years): 32 Gender: M Diabetes duration (years): 18	Insulin needle injection	Detection Palpation, US Assessors ND Region Abdomen	Change in LH, diabetes-related outcomes: HbA1c, insulin use, hypoglycaemic episodes
Perciu et al. (2012) [32] Romania	Analyse cutaneous and subcutaneous dystrophies using two different ultrasounds	Patient 1 Population: Diabetes (NS) Age (years): 55 Gender: M Diabetes duration (years): ND	Insulin needle injection	Detection Physical examination, US Assessors ND Region Abdomen	Presence of cutaneous damage, metabolic control
		Patient 2 Population: Diabetes (NS) Age (years): 30 Gender: F Diabetes duration (years): ND	CSII	Detection US Assessors ND Region ND	

CD cannot determine, CSII continuous subcutaneous insulin infusion, F female, HbA1c glycated haemoglobin, HPs health professionals, LH lipohypertrophy, M male, MDI multiple dose injection, ND no data, NS not specified, RCT randomised controlled trial, T1DM type 1 diabetes mellitus, T2DM type 2 diabetes mellitus, US ultrasound

^a Primary or longest mode of insulin delivery

LH Prevalence, Anatomical Distribution and Tissue Morphology

Nine studies assessed the prevalence of LH lesions. The prevalence of LH ranged from 14.5% to 88%, with a median estimate of 56.6% (Table 2). Two studies considered prevalence in the context of continuous subcutaneous insulin infusion (CSII) delivery and reported respective prevalences of 44% and 76% [21, 26].

Seven studies examined the anatomical distribution of LH sites, with the abdomen, thighs and arms being the most frequently identified (Table 3). Less common areas were the back, buttocks and hips [14, 19–21, 23, 25, 29].

Characterisation of LH Using US

In terms of tissue morphology, the reported characteristics showed mainly increased echogenicity in diffuse areas of the injected subcutaneous tissue, some with clearly defined nodules of different sizes embedded within the area with circumscribed margins [19, 24, 27, 28, 33]. Kapeluto et al. [33] define this further as nodules not having a capsule or vascularity, which differentiates the US signature of LH from haematomas or fluid-filled

cysts, which do have capsules. In some cases, the centre or part of these LH nodules could be hypoechogenic possibly representing fluid from oedema or fat necrosis [19, 27, 28]. Perciun and Mihiu [28] also showed reduced echogenicity when the sites had been rested for 6 months, suggesting dissipation of the LH, but not in all cases and particularly not in those showing greater fibrosis of the fat tissue (echogenicity), or in those with possible necrosis at baseline scan. The study by Perciun and Mihiu [28], which included 10 children (19% of the cohort), reported the presence of LH in cases with insulin exposure of as little as 2–5 months. Thickening of the dermal layer and loss of a clear delineation between the subcutaneous and dermal layer at the injection site was noted in two papers and was identified as a potential inflammatory response to repeated insulin exposure [24, 27].

Four studies attempted to classify LH into types or grades of LH [19, 24, 27, 33]. Perciun [27] included five levels for LH grading: (1) nearly normal, (2) diffuse echogenicity (fibrous tissue) with no well-defined delineation between dermis and subcutis, (3) focal areas within this tissue (nodules within diffuse areas), (4) focal areas with hypoechogenic halos within the nodules, a thickened dermal layer and loss

Table 2 Prevalence of LH depicted by different detection methods

Author (year)	Insulin therapy ^a	LH prevalence (%) based on detection method		
		US	Palpation	Not specified
Blanco et al. (2013) [20]	Pen	64.4		
Conwell et al. (2008) [21]	CSII		44.0	
Davidenko et al. (2014) [22]	NS			84.0
Gentile et al. (2016) [14]	Needle injection			48.8
Nasser et al. (2017) [25]	Needle injection	36.8		
Patrakeeva et al. (2014) [26]	CSII, MDI	76.0		
Perciun (2010) [27]	Needle injection			88.0
Volkova et al. (2013) [29]	Needle injection	86.5	37.0	
Wang et al. (2014) [30]	Needle injection	14.5		

CSII continuous subcutaneous insulin infusion, LH lipohypertrophy, MDI multiple dose injection, US ultrasound

^a Primary or longest mode of insulin delivery

Table 3 Regional distribution of LH

Author (year)	Insulin therapy ^a	Anatomical distribution of LH			
		Abdomen	Arm	Thigh/gluteus	Other
Bertuzzi et al. (2017) [19]	CSII, MDI	100% (US, Palp.)	25.0% (US), 20.0% (Palp.)	25.0% (US), 20.0% (Palp.)	
Blanco et al. (2013) [20]	Pen	ND ^b			
Conwell et al. (2008) [21]	CSII	SS: 6.1 ± 3.3		SS: 4.9 ± 4.2	
Gentile et al. (2016) [14]	Needle injection	40.0%	35.0%	25.0%	
Kasperska-Czyzyk et al. (2000) [23]	Needle injection	61.8%	17.6%	20.6%	
Nasser et al. (2017) [25]	Needle injection	S/SC: 3.1/23.3 mm	S/SC: 2.9/12.3 mm	S/SC: 3.2/12.3 mm	
Volkova et al. (2013) [29]	Needle injection				Paraumbilical/buttocks: 61.0% Paraumbilical/buttocks + hips: 15.0% Paraumbilical/buttocks + shoulders: 11.0%

CSII continuous subcutaneous insulin infusion, LH lipohypertrophy, MDI multiple dose injection, ND no data, Palp. palpation, S/SC skin/subcutaneous thickness, SS severity score, US ultrasound

^a Primary or longest mode of insulin delivery

^b Authors report that LH sites were most commonly observed in the abdomen

of delineation between the dermis and subcutis layers, (5) nodules with a hypoechogenic necrotic or liquid-filled areas and thickened dermis. More recently, Mulnier et al. [24] further identified a four-level grading scale of LH based on the presence of diffuse areas, nodule size, nodule number and inflammatory changes. Bertuzzi et al. [19] characterised LH on the basis of hyperechogenic regions with prevailing fibrosis, hypoechogenic areas and mixed hypo/hyperechogenicity.

Risk Factors of LH

Five studies considered associations between injecting behaviours and patient characteristics

with the presence of LH (Table 4). These findings suggest higher prevalence of LH in relation to the level of site rotation, frequency of injections, needle reuse, needle injection at 90°, injection in the arm and abdomen, and a lower level of general education.

Sensitivity of LH Detection Methods

Four studies compared physical assessment of LH with US detection. The methods used for physical examination varied and included both visualisation and different palpation protocols. Only one of four studies used prespecified criteria to examine areas of LH, including either features of hyperechogenic (fibrosis) or

Table 4 Risk factors of LH

Author (year)	Risk factors of LH	Statistical value
Blanco et al. (2013) [20]	Needle reuse	$P = 0.008$
	Patient-reported injection site rotation	$P = 0.001$
	Nurse-reported injection site rotation	$P = 0.0001$
	Nurse observed + patient claimed injection site rotation	$P = 0.0001$
Conwell et al. (2008) [21]	BMI z-score 0.60 ± 0.76	$r = -0.3, P = 0.04$
	Needle insertion angle at 90°	$P = 0.03$
Davidenko et al. (2014) [22]	Insulin use	AUC > 0.5–86.0%
Nasser et al. (2017) [25]	Level of education	$P = 0.02$
	Number of injections	$P = 0.02$
	Injection site: Arm	$P = 0.04$
	Injection site: Abdomen	$P = 0.001$
Patrakeeva et al. (2014) [26]	Glucose variability	$r = 0.8$
	Incorrect insulin injection technique/infusion set changing	$r = 0.7$

AUC area under the curve, BMI body mass index, LH lipohypertrophy

hypoechoic (oedema/fluid) lesions [19]; whilst the remaining studies were preliminary and did not mention their protocol in detail. The methods used for palpation detection of LH varied considerably and included a palpable increase in subcutaneous fat [23], an extended version of the FIT guidelines involving a pinch technique to compare the thickness of harder skin to adjacent areas of skin [14], and another examined the shape irregularity of LH areas, as well as assessing texture consistency and area of LH extension [19]. As a result of inconsistencies in protocol design in detection tools across the studies, the estimations of LH prevalence varied between studies. One study reported that palpation detected 64% more LH regions compared to US [23]. Conversely, Volkova et al. [29] reported that US scanning detected 56% more LH lesions than with palpation alone. One study included a comparison between routine palpation and palpation by nurses trained to identify LH lesions through a detailed stringent tactile palpation technique with US [14]. They found that while standard palpation methods detected 66% of the US identified lesions, the additionally trained nurses detected 96% of

lesions. The fourth study identified overall equivalence in the detection of LH between US and palpation [19]. However, they found that US was able to detect more sites in the arm and gluteus regions than palpation [19]. This study also reported high precision in the US-assessed LH region in relation to the size and distribution of the affected areas. The area of lipohypertrophic extensions was noted to be 5 cm² bigger with US ($\sim 35 \pm 10$ cm²) than that recorded by palpation and inspection ($\sim 30 \pm 15$ cm²), suggesting increased sensitivity [19].

DISCUSSION

This is the first systematic review of studies of US assessed LH. The review has identified some potentially important new insights into the distribution and characteristics of LH based on US examination. In terms of regional distribution, LH was predominantly localised in the abdomen, a finding consistent with palpation and possibly associated with patient preference for the abdomen as an injection site. The studies

using US to characterise LH provide a much more detailed perspective on the size and depth of tissue changes observed following repeated insulin exposure and available tissue, suggesting that US could be used to optimise needle length selection.

Findings relating to the comparison between palpation and US for LH sites illustrate a discrepancy in the detection of these sites with one study reporting that palpation produces 65% more false positive results [23], while another demonstrates that US detects 50% more LH cases [29]. It is conceivable that deficits in LH detection reported for palpation are related to inadequate technique. While more rigorous guidelines have been established, most notably the FIT guideline in 2010 [34] which are observed in many countries [35], it was noted that this approach was inferior to an even more rigorous method of palpation with a 60% higher rate of detection [14]. This result may suggest that a rigorous palpation method may be as sensitive as US and if adopted clinically would limit the need to use US in clinical care. However, US has additional advantages over palpation as it can better assign the nature and severity of LH in much more detail compared to palpation, enabling greater granularity in grading the LH (size, distribution and elasticity) [19, 24, 28, 33] and thus giving clinicians the opportunity to give more detailed advice to patients. Through visualisation of the LH tissue, US images may encourage injection behaviour changes by revealing areas of disrupted tissue, inflammation and depth of subcutaneous tissue. This could help inform choice of needle length and reinforce the importance of site rotation and single needle use. Future detailed clinical studies of the impact of the differing types and grades of LH on the insulin action curve and glucose variability could be highly valuable and informative clinically. From a behaviour change perspective, the patient visualising the injection sites on US may act as a strong cue to move sites as well as choose appropriate needle lengths and new injection areas with optimal insulin absorption and action. Overall, the use of US could encourage and reinforce injection techniques, which could support and improve effective self-management

of diabetes and help minimise the risk of long-term complications. Finally, the incorporation of US into routine clinical care in the context of the annual review may ensure that LH is screened more objectively, precisely and rigorously.

Strengths and Limitations

As with all reviews, the level of insight gained is predicated by the quality of the evidence and methods of the source studies. There are some shortcomings in the quality of the included studies. A particular weakness was in relation to the studies comparing palpation and US in LH assessment, where there was a high level of heterogeneity in the detection methods observed which may confound the results. Moreover, the lack of detail on the clinician's training level to detect LH may affect the validity of the findings. However, we were able to extrapolate from these studies some important insights into LH by integrating the study findings. Nonetheless, this review has highlighted some important details on the nature of LH and the potential of US in its detection and management, paving the way for further inquiry into this important and neglected aspect of diabetes care.

Implications for Future Research

Currently, there are limited studies that present data on LH detection accuracy from palpation and US assessment. Conducting RCTs that include nurse training to implement the extended FIT guidelines for palpation techniques and interpretation of echogenic US scans of LH sites would provide more credible comparative results on the reliability and sensitivity of each detection method. In addition, economic evaluation of the diagnostic sensitivity of the different methods would ascertain the cost-effectiveness of each. Lastly, information on staff and patients' experiences of LH detection and site management in the avoidance of LH could help us better understand patient injection preferences as well as design a site management method that would help avoid the

build-up of LH and help prevent it in those new to treatment with insulin in the future.

CONCLUSION

The current literature emphasises the knowledge gap in the sensitivity, reliability and accuracy of the different tools used to detect the presence of LH. The existing research highlights the need for further and more robust clinical research to evaluate the feasibility and cost-effectiveness of US in comparison to palpation. Nonetheless, the overall evidence implicates that US scans may provide more accurate results than palpation alone and can report more explicit detailed information that could prompt effective education on injection and site management practices that could potentially improve self-management and diabetes outcomes. The dynamic shift to e-health aimed at improving efficiency and accuracy suggests that introduction of US scanning for LH assessments in routine care is foreseeable.

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